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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,733	11/08/1999	ALPHONSE GALDES	CIBT-P02-052	5606

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	36

DATE MAILED: 04/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/435,733	Applicant(s) Galdes et al.
	Examiner Michael Brannock	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 13, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6, 9-53, 55, and 59-73* is/are pending in the application.

4a) Of the above, claim(s) *12, 24-29, 32-40, 42, 43, and 49* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 9-11, 13-23, 30, 31, 41, 44-48, 50-53, 55, and 59-73* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. The request filed on 01/13/03 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant is notified that the amendments put forth in Paper 28, 01/13/03, have been entered in full.

3. Claims 1-6, 9-53, 55, and new claims 59-73 are pending.

4. Claims 12, 24-29, 32-40, 42, 43, and 49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, as set forth in Paper 18, 8/15/01. Additionally, as set forth in Paper 18, claims 1-6, 9-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50-53, 55, 59-73 will be examined only to the extent that the claims are directed to methods of treatment of diabetic neuropathy comprising the administration of a sonic hedgehog polypeptide, as per Applicants' election in Paper 17.

5. Applicant is notified that any outstanding rejection that is not expressly maintained in this Office Action has been withdrawn.

Maintained Rejections:

6. Claims 1-6, 9-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50-53, 55, 59-73 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 7 of Paper 20, and recast in view of Applicant's amendments below. The specification, while being enabling for methods of treating and protecting against cisplatin and taxol induced neuropathy and a neuropathy resulting from sciatic nerve crush, or viral induced neuropathy comprising the systemic administration of sonic hedgehog polypeptide, wherein the polypeptide is modified at the either the C-terminal or N-terminal amino acid residue, does not reasonably provide enablement for the treatment for or protection against other neuropathies, nor for the treatment of any neuropathy comprising the systemic administration of a hedgehog agonist other than a polypeptide 100% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, nor for internally modified hedgehog proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents the results obtained in several experimental neuropathic models, wherein sonic hedgehog is systemically administered (subcutaneous (s.c.) administration). Systemic administration of Sonic hedgehog appeared to be effective in several of the models, e.g. cisplatin and taxol induced neuropathy (page 24) and rat sciatic nerve crush injury (page 79). However, in the other cases, it is unclear if administration of sonic hedgehog has a measurable beneficial effect. In the example of the SOD deficient mice no significant

differences were found after treatment of male mice (page 77). Further, in the galactose model of neuropathy, it is unclear if any difference between the groups is significant (Figure 23). Additionally, treatment of diabetic rats with sonic hedgehog does not appear to have been attempted. Thus, it is unclear based on the teachings of the specification, which of the multitude of neuropathic disorders contemplated are amenable to treatment with sonic hedgehog or any other hedgehog agonist.

Subsequent to the filing of the instant application, several groups, including one of the instant inventors, reported limited success with systemic administration of sonic hedgehog in the treatment of peripheral neuropathies. Welty et al., *Soc. Neurosci. Abs.* 27(2)pp2621, 2001, report that systemic administration of sonic hedgehog did not alter the disease course in transgenic ALS mice. Further, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of peripheral neuropathies, only certain neuropathies are amenable to treatment (e.g ALS is not) and of those that are (e.g. sciatic nerve crush), the specificity of the hedgehog agonist is critical, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Thus, it is unclear which of the multitude of neuropathic disorders contemplated are amenable to systemic treatment with sonic hedgehog or any other hedgehog agonist, and of those

that are amenable to treatment with sonic hedgehog, it is unclear what other hedgehog agonists could be used systemically.

Applicant argues that the specification clearly contemplates the treatment of a range of peripheral neuropathies and provides a working example of the treatment of one such neuropathy. Applicant further notes that post-filing date evidence demonstrates that other neuropathies are amenable to treatment as well. This argument has been fully considered but not deemed persuasive. While it is true the specification contemplates the treatment of other forms of neuropathy, the specification simply provides the speculation that hedgehog proteins would be effective in the treatment of these neuropathies. In fact, most, if not all, peripheral neuropathies are contemplated by the specification as being amenable to treatment with hedgehog proteins. It is well appreciated in the art, and acknowledged in the specification at page 1 that neuropathy is a generic term used to describe a broad array of disparate disorders that are known to result from about 200 different causes. The claims are directed to multiple forms of neuropathy, each being recognized in the art as being distinct, having divergent etiologies and requiring divergent treatments - some having no effective treatments available at all, as is discussed in the specification at pages 1-17. Importantly, the art does not recognize that any particular treatment that is known to be effective for one form of neuropathy is effective for the treatment of neuropathy in general. The specification provides essentially two types of neuropathy that are amenable to treatment, e.g. chemotherapeutic drug induced neuropathy and neuropathy resulting from nerve crush. The highly skilled artisan would thus appreciate that these examples could not

be expected to be representative of neuropathies in general. Instead, the highly skilled artisan would appreciate that the contemplations of the specification amount to no more than an invitation to begin a research plan to try to find other neuropathies that are amenable to treatment.

The post-filing date examples, e.g. the Allendoefer Declaration, are exactly the type of extensive research and investigation required and referred to above. Importantly, none of the examples provide evidence that hedgehog protein is effective for the treatment of neuropathy in general. To the contrary, Welty et al., *Soc. Neurosci. Abs.* 27(2)pp2621, 2001, report that systemic administration of sonic hedgehog did not alter the disease course in transgenic ALS mice. Further, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of peripheral neuropathies, only certain neuropathies are amenable to treatment (e.g ALS is not) and of those that are (e.g. sciatic nerve crush), the specificity of the hedgehog agonist is critical for some unknown reason, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not. Thus, it is unclear based, on the teachings of the specification, which of the multitude of neuropathic disorders contemplated are amenable to treatment with sonic hedgehog or any other ptc therapeutic. Additionally, as set forth previously, Oppenhiem *et al. Mol. Cell. Neuroscience* 13(348-361)1999 reported mixed results with the administration of sonic hedgehog

in the treatment of a variety of different neuronal populations. Oppenhiem *et al.* report that the administration of exogenous sonic hedgehog to embryos *in vivo* or to motor neuron cultures failed to promote the survival of several different neuronal population including spinal motor neurons, spinal interneurons, sympathetic preganglionic neurons, sensory neurons and neuronal precursors (see the Abstract). Further, Oppenhiem *et al.* were "surprised to discover that Shh failed to promote the survival of chick embryo spinal chord cells and actually induced the death of apparent neuronal and floor-plate cells during the first stage of spinal chord programmed cell death" (see page 353, col. 2). Additionally, as discussed previously, in mice, Miao et al. found that "neurons of the peripheral nervous system show no survival in response to sonic hedgehog administration" (see page 5898, col 1, 2nd and 3rd paragraphs, of Miao et al.) Thus, it is unclear which types of peripheral neuropathies are amendable to treatment. The specification has merely provided to the skilled artisan an invitation to begin further research and investigation into which other of the multitude of pathologies involving the motor and/or sensory nervous systems could ultimately be treated as claimed; and then to begin further research and investigation into the particular methodologies of administration and treatment schedule that would be required once and amendable disorder has been identified. The specification has provided no guiding principle to identify which particular neuropathies would be amendable to treatment, and nor is such a principle known in the art. The skilled artisan is therefore left to undergo extensive random trial and error experimentation in order to determine which neuropathologies are amendable to treatment.

Applicant provides a multitude of examples wherein one species of sonic hedgehog protein is effective in another species, and concludes that hedgehog signaling is tolerant to some variation in the sequence of the hedgehog protein. This argument has been fully considered but not deemed persuasive. First, Applicant is reminded that the claims have been indicated to be enabled for sonic hedgehog from each of the disclosed species (see above). Second, regarding the concept of signaling being tolerant to sequence variation, there is variation between the naturally occurring sonic hedgehog proteins, referred to in Applicant's examples; yet this variation has occurred under the constraint of over 100 million years of selective pressure during the evolution of these species. These differences have arisen through random mutation, and those that did not function have been eliminated. The specification has provided little more than this strategy of evolution to guide the artisan in the construction of mutants that will function as required. The artisan is simply invited to embark on an essentially random trial and error process of experimentation wherein amino acids are substituted/added/deleted from the parent sequence and then assayed for activity to try to find variants that work. Third, the claims stipulate that the protein be required to have some effect on nerve cells, yet the specification has not provided a rapid assay such that the artisan would expected that screening for variants would be routine. Thus, the extensive experimentation required to make and test the genus of mutants encompassed by the claims is unduly burdensome.

Applicant's arguments, as they are intended to relate to enablement for variant polypeptides, regarding the number of inoperable embodiments that are allowed to be

encompassed by a claim are unpersuasive because the issue is that the specification has failed to teach how to make operable embodiments without undue experimentation.

Additionally, while being enabling for the claimed methods comprising administering the N-terminal autoproteolytic fragment of sonic hedgehog wherein the protein is modified at the N-terminal amino acid residue, does not reasonably provide enablement for method comprising the administration of sonic hedgehog modified with a lipophilic moiety at an internal residue. specification provides no guidance as to which internal residues would be amenable to lipophilic modification. One skilled in the art would appreciate that lipid modification of an internal residue in the polypeptide completely changes the chemical identity of that residue. The specification provides only an invitation to perform random trial and error experimentation to identify which internal residues, if any, are amenable to change. Such extensive experimentation is unduly burdensome. Further, the art recognizes the difficulty in determining the effect of lipid modification on an internal residue, e.g. WO 95/18856 (Ingham et al.) at page 34, and Jonassen et al. (e.g. page 2, lines 14-20), each teach that the lipophilic moiety be attached to either the N or C-terminal of the peptide. Nor, has the specification taught which fragments of sonic hedgehog would work as claimed. The specification has simply invited the artisan to begin an extensive research plan to randomly make and test fragments to try to find fragments that work as claimed. Such extensive experimentation is unduly burdensome.

7. Claims 1-6, 9-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50-53, 55, 59-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and recast below in view of Applicant's amendments.

The claims require *in vivo* methods of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves comprising systemically administering a "therapeutic amount" or an "effect amount" of a hedgehog polypeptide at least 80% identical to sonic hedgehog or a polypeptide that is encoded by a polynucleotide that hybridizes to a sonic hedgehog encoding polynucleotide. However one skilled in the art would not know which, if any, other than sonic hedgehog has the property of being efficacious for systemic administration in the treatment of peripheral neuropathies. There appears to be no description of such a particular protein, nor guidance as to what structural characteristics such proteins must possess, nor are such known in the art. Nor has the specification put forth what structural characteristics a protein may have that allows it to function in the claimed method, yet also be structurally different than sonic hedgehog. As discussed above, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog in the treatment of peripheral neuropathies, the specificity of the hedgehog agonist is critical in some unknown way, e.g. sonic and desert

hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not. Applicant has not provided a guiding principle to allow one skilled in the art to know which hedgehog proteins, other than a naturally occurring sonic hedgehog protein, are effective in treating any peripheral neuropathy.

New Rejections:

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-6, 9-11, 13-31, 41, 44-48, 50-53, 55, 70-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims require lipophilic modification at "an" N-terminal residue. The presence of the words "an" and "a" render the claims indefinite because it is unclear if the claims are referring to "the" N-terminal residue or if the claims refer to any residue that might be considered to be in the N-terminus of the protein. If it is the latter case, then the claims are also indefinite because the specification has not set forth which residues make-up the N-terminus.

10. Claims 1-6, 9-11, 13-31, 41, 44-48, 50-53, 55, 70-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims require a lipid modification that comprises addition of two or more lipophilic moieties to an N-terminal amino acid residue. There does not appear to be any mention of this embodiment in the specification as filed, and nor would it be reasonably inferred by the skilled artisan that Applicant had contemplated such an embodiment at the time of filing.

11. The amendment filed 1/13/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: as set forth above, claims 1-6, 9-11, 13-31, 41, 44-48, 50-53, 55, 70-73 require a lipid modification that comprises addition of two or more lipophilic moieties to an N-terminal amino acid residue. There does not appear to be any mention of this embodiment in the specification as filed .

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 8, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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